#17 YC 6-1-01

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By: Nancy Glynn Printed: Nancy L. Glynn

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	Hillman et al.		
Title:	NOVEL HUMAN MITOCHONDRIAL MEMBRANE PROTEIN		
Serial No.:	09/208,619	Filing Date:	December 8, 1998
Examiner:	Harris, A.	Group Art Unit:	1642

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BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed March 15, 2001, received by the PTO on March 19, 2001, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the statutory fee of $310.00 for the filing of this Brief. This Appeal Brief is filed on time because May 19 is a Saturday.

This is an appeal from the decision of the Examiner finally rejecting claims 17, 18, and 32 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc., now Incyte Genomics, Inc. (Reel 8951, Frame 0923) who is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 17, 18, and 32
Claims allowed:	(none)
Claims canceled:	Claims 1-16
Claims withdrawn:	Claims 19-31 and 34-43
Claims on Appeal:	Claims 17, 18 and 32 (Copy of claims on appeal, as amended in the enclosed second Amendment after Final, in attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

The Amendment after Final Rejection under 37 C.F.R. §1.116 filed February 15, 2001, has been entered for purposes of this appeal. See the Advisory Action mailed March 6, 2001, indicating the Amendment would be entered upon filing of an appeal.

The amendments and arguments filed February 15, 2001, have overcome the rejections of claims 32 and 33 under 35 U.S.C. § 112, first and second paragraphs, and the rejections of claims 17 and 18 under 35 U.S.C. § 101 and § 112, first paragraph.

Appellants have also submitted a second Amendment after Final Rejection which is believed to overcome the remaining rejections and objections.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a polypeptide sequence termed HuTIM17, the sequence of which is disclosed in SEQ ID NO:1. HuTIM17 shares extensive amino-acid-identity with human preprotein translocase and with yeast mitochondrial inner membrane protein 17. In particular, HuTIM17 and human preprotein translocase share 75% amino acid sequence identity; HuTIM17 and yMIM17 share 48% amino acid sequence identity (Fig. 2). As illustrated by Figs. 3 and 4, HuTIM17 and yMIM17 have similar hydrophobicity plots. HuTIM17 has potential transmembrane domains comprising amino acids 16 to 34, 63 to 82, and 94-135 of SEQ ID NO:1; the latter domain is of sufficient length to span the membrane twice. (Specification, page 12, lines 10-20.) Furthermore, as disclosed in the specification on page 12, lines 17-20, Northern analysis shows the expression of HuTIM17 in libraries prepared from a wide variety of cells and tissues, including brain, prostate, melanocytes, pancreas, bladder, lymph node, leukocytes, liver, colon, thyroid, kidney, synovium, heart, lung, and breast. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require detailed knowledge of how the polypeptide coded for by the

polynucleotide works. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

(6) ISSUES

1. Whether or not claims 17 and 18, on appeal, are unpatentable under 35 U.S.C. §112, first paragraph, for reason that the invention is not described in the specification and/or particularly pointed out by the claims.

2. Whether or not claims 17 and 32, on appeal, are unpatentable under 35 U.S.C. §102(b) or §103 for being anticipated or obvious over Accession Numbers P39515, Q02310, Maarse et al., Ryan et al., and U.S. Patent #5,876,991 in view of Harlow and Lane.

(7) GROUPING OF THE CLAIMS

As to Issue 1

This issue pertains only to claims 17 and 18.

As to Issue 2

This issue pertains only to claims 17 and 32.

(8) APPELLANTS' ARGUMENTS

Issue 1 - Whether the claims as directed to biologically and immunologically active fragments are adequately described under 35 U.S.C. § 112, first paragraph.

The Examiner's Rationale:

Claims 17 and 18 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description. The Examiner asserts that Appellants "have yet to define what specific amino acid should be designated as "biologically active" and "immunologically active" fragments. Applicants have yet to express where the biologically-activity [sic] resides in the claimed fragments." (Advisory Action, page 1.)

Argument:

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.* *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

First note that the "fragment" language of independent claim 17, as amended by the Second Response after Final Rejection, recites "a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said biologically-active fragment is imported into the inner mitochondrial membrane", and "an immunologically active fragment of the amino acid sequence of SEQ ID NO:1, wherein said immunologically active fragment comprises at least 10 contiguous amino acids of SEQ ID NO:1 and generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1."

The amino acid sequence of SEQ ID NO:1 is explicitly disclosed in the specification. See, for example, Figure 2. At, for example, pages 12, lines 9-20, the Specification describes the chemical and structural characteristics of the polypeptide of SEQ ID NO:1 (HuTIM17). The polypeptide and fragments thereof can be produced by either recombinant means (see, *e.g.*, the Specification at page 16, line 17 through page 17, line 13; and pages 18-22) or by chemical synthesis (see, *e.g.*, the Specification at page 17, lines 16-21; and page 24, lines 15-21).

Note that at page 6, lines 21-25, biologically active is defined as "a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule" and "immunologically active" is defined as "the capability of the natural, recombinant, or synthetic HuTIM17, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific

antibodies." Specific binding is further defined at page 10, lines 15-21, as meaning that:

> . . . in reference to the interaction of an antibody and a protein or peptide, mean[s] that the interaction is dependent upon the presence of a particular structure (i.e., the antigenic determinant or epitope) on the protein; in other words, the antibody is recognizing and binding to a specific protein structure rather than to proteins in general. For example, if an antibody is specific for epitope "A", the presence of a protein containing epitope A (or free, unlabeled A) in a reaction containing labeled "A" and the antibody will reduce the amount of labeled A bound to the antibody.

Methods of producing specifically binding antibodies are described, for example, at pages 26-28. The specification indicates that "[i]t is preferred that the peptides, fragments, or oligopeptides used to induce antibodies to HuTIM17 have an amino acid sequence consisting of at least five amino acids, and more preferably at least 10 amino acids" (Specification, page 26, line 29 through page 27, line 1). See also pages 47-48 which describe the production of antibodies to fragments of HuTIM17, including the description of how to identify appropriate immunogenic sites of HuTIM17:

> The amino acid sequence deduced from SEQ ID NO:2 is analyzed using DNASTAR software (DNASTAR Inc) to determine regions of high immunogenicity, and a corresponding oligopolypeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions, is described by Ausubel et al. (supra), and others. (Specification at page 47, lines 21-25)

Furthermore, the Specification describes methods for determining the biological activity of HuTIM17 by assaying its import into the mitochondrial inner membrane, at pages 46-47. The localization of a membrane protein such as HuTIM17 depends in part upon the presence of transmembrane domains. The potential transmembrane domains of HuTIM17, polypeptide fragments comprising amino acids 16 to 34, 63 to 82, and 94 to 135 of SEQ ID NO:1 are described in the Specification at page 12, lines 15-17).

Given the "blueprint" provided by SEQ ID NO:1, and the detailed guidance set forth by the Specification, the structure of fragments of SEQ ID NO:1 is apparent and there is no need to explicitly list the sequences of the numerous possible fragments. Such a list would just needlessly clutter the Specification.

Thus the disclosure of the instant application satisfies the written description requirements under 35 U.S.C. § 112, first paragraph, based on the literal disclosure in the specification and what was known in the art at the time the application was filed. For at least these reasons, the rejection should be withdrawn.

Issue 2 – Whether claims 17 and 32 are anticipated under 35 U.S.C. § 102(b) or obvious under 35 U.S.C. § 103 by Accession Numbers P39515 and Q02310, Maarse et al., Ryan et al., and U.S. Patent #5,876,991.

The Examiner's Rationale:

Claim 17 stands rejected under 35 U.S.C. 102(b) as allegedly anticipated by various references including Accession Numbers P39515 and Q02310, Maarse et al., Ryan et al., and U.S. Patent #5,876,991. Claim 32 stands rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over the above references in view of Harlow and Lane. Appellants have previously pointed out, in the Response to Final Office Action filed February 15, 2001, that the references all disclose a yeast MIM17, which shares homology with SEQ ID NO:1 in regions of six consecutive amino acids at most (see, for example, Figure 2) and thus would lack the transmembrane domains required for successful insertion into the mitochondrial membrane. The Examiner has asserted that "these points are not recited in the claims, hence do not absolve the art rejections of claims 17 and 32". The Examiner has further asserted that this statement "is Applicants' opinion and not an established fact", and that "[t]here is no fact pattern presented by Applicants that the referenced fragments would not inherently retain the activities as listed in the claims." (Advisory Action, page 1). With respect to immunologically active fragments, the Examiner asserts that "four amino acids is defined as an epitope, thus immunologically active" (Advisory Action, pages 1-2).

Argument:

As amended by the Second Response after Final Rejection, claim 17(c) now recites "a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said biologically-active fragment is imported into the inner mitochondrial membrane". The specification describes methods for determining the biological activity of HuTIM17 by assaying its import into the mitochondrial inner membrane at, for example, page 46, line 24 through page 47, line 16. Thus the claims as amended specifically incorporate the requirement that the claimed fragments can be imported into the inner mitochondrial membrane. Since the reference fragments, lacking transmembrane domains, cannot be successfully imported, they do not anticipate.

Appellants also respectfully point out that the requirements for transmembrane domains in

membrane proteins are well known in the art, and are discussed in, for example, the enclosed reference, S.J. Singer, "The structure and insertion of integral proteins in membranes" Annu. Rev. Cell Biol. (1990) 6:247-296. As Singer discloses, "essentially all integral proteins known at present appear to be TM molecules" (page 267). The characteristic transmembrane domain is 15-25 hydrophobic amino acid residues in length (page 253), and in fact the mechanism of insertion into the membrane requires a hydrophobic stretch of at least about 20 amino acid residues (pages 272-273). The reference fragments would be at best six amino acids in length, and thus would be immediately recognized by one of skill in the art as simply being too short to serve as transmembrane domains. Since the ability to be inserted into a membrane is explicitly required of the claimed biologically active fragments, the reference fragments do not anticipate the claims.

With respect to the claimed immunologically active fragments, Appellants note that claim 17(d), as amended by the Second Response after Final Rejection, now recites "an immunologically active fragment of the amino acid sequence of SEQ ID NO:1, wherein said immunologically active fragment comprises at least 10 contiguous amino acids of SEQ ID NO:1 and generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1." The specification explicitly states, at page 26, line 29 through page 27, line 1, that "[i]t is preferred that the peptides, fragments, or oligopeptides used to induce antibodies to HuTIM17 have an amino acid sequence consisting of at least five amino acids, and more preferably at least 10 amino acids." Since none of the references disclose fragments comprising at least 10 contiguous amino acids of SEQ ID NO:1, they do not anticipate the claims.

Thus the cited references do not disclose the claimed fragments having the recited activities, and therefore fail to anticipate claim 17. Nor are compositions comprising the fragments, as in claim 32, made obvious by the references in view of Harlow and Lane, since Harlow and Lane is a general reference on antibody methods and does not disclose the claimed fragments. For at least the above reasons the rejections of claims 17 and 32 under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) should be withdrawn.

(9) CONCLUSION

Appellants respectfully submit that the Specification provides an adequate written description of the claimed subject matter, and the meaning of the claims is clear. Hence, the rejections based on the first paragraph of 35 U.S.C. §112 should be reversed.

Furthermore, the claims are not anticipated or made obvious by the polypeptides of Accession Numbers P39515 and Q02310, Maarse et al., Ryan et al., and U.S. Patent #5,876,991, and therefore the

rejections based on 35 U.S.C. §102(b) and 35 U.S.C. § 103 should be reversed as well.

Due to the urgency of this matter and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This form is enclosed in ~~triplicate~~. duplicate

Respectfully submitted,

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APPENDIX

Claims on Appeal:

17. A purified polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:1,

b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1,

c) a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said biologically-active fragment is imported into the inner mitochondrial membrane, and

d) an immunologically active fragment of the amino acid sequence of SEQ ID NO:1, wherein said immunologically active fragment comprises at least 10 contiguous amino acids of SEQ ID NO:1 and generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1.

18. An isolated polypeptide of claim 17, having a sequence of SEQ ID NO:1.

32. A composition comprising a polypeptide of claim 17 and a pharmaceutically acceptable excipient.